ARGUMENTS/REMARKS

Status of the Claims

Claims 33-79 and 81-97 are currently pending in the present application. Claims 1-32 and 80 have been canceled, and claims 33-52, 54-79 and 81-86 have been withdrawn as being drawn to a nonelected invention. Claim 53 is rejected for the reasons stated in the Office Action of December 2, 2011.

Amendments to the Claims

Claim 33 is amended in the present communication to clarify the invention. The amendments do not include new matter and their entry is respectfully requested.

The Invention

The invention is directed towards a method for isolating a microRNA of interest from a sample with the microRNA of interest. First, a sample with the microRNA of interest is combined with a capture probe, and first linker and second linkers. The capture probe has: i) a first adapter segment having a first adapter segment sequence, the first adapter segment having a 3' end and a 5' end; ii) a second adapter segment having a second adapter segment sequence, the second adapter segment having a 3' end and a 5' end; and a microRNA binding segment having a microRNA binding segment sequence. The microRNA binding segment of the capture probe is substantially complementary to, and capable of hybridizing to, one or more than one microRNA of interest by Watson-Crick base pairing. The 5' end of the first adapter segment is connected to the 3' end of the microRNA binding segment, and the 3' end of the second adapter segment is connected to the 5' end of the microRNA binding segment.

Second, after the sample with the microRNA of interest, the capture probe, and first linker and second linkers are combined, the first linker hybridizes with the first adapter segment, the microRNA of interest hybridizes with the microRNA binding segment, and the second linker hybridizes with the second adapter segment.

Third, the 3' end of the first segment is ligated to the 5' end of the microRNA of interest, and the 3' end of the hybridized microRNA of interest is ligated to the 5' end of the hybridized

second linker. This complex is defined as a strand of first linker, microRNA of interest and second linker that have been ligated together (ligated first linker- microRNA of interest-second linker) and hybridized to the capture probe;

Fourth, the capture probe is dehybridized from the strand of the ligated first linker-microRNA of interest-second linker.

Fifth, the ligated first linker- microRNA of interest-second linker is purified from the capture probe, thereby purifying the microRNA of interest.

The invention contemplates that a set of capture probes with different microRNA binding segments is used. The set has a first capture probe and a second capture probe with different first and second adaptor segment sequences.

Claim Rejections

35 USC §112, 1st Paragraph

The Office Action rejected Claim 53 under 35 USC §112, 1st paragraph as failing to comply with the written description requirement. In particular, the Office Action alleges that the phrase "phosphorothioate backbone" as found in claim 33, from which claim 53 depends, has no support in the original specification and is therefore considered to be new matter.

Applicants respectfully disagree. This limitation can be found in, for example, paragraphs [0024] and [0026] of the specification, as well as claim 58 as originally filed.

35 USC §103

Claim 53 is rejected under 35 §103(a) as being unpatentable over Jacobsen et al. (US 2005/0272075) in view of Shapero et al (US 2005/0153347) and Baracchini et al (US Pat. No. 5,801,154). Applicants respectfully disagree.

The Office Action alleges that the Jacobsen reference does not teach a set of capture probes that target different microRNA molecules. While Applicants agree with the Office that the Jacobsen reference does not teach a set of capture probes that target different microRNA molecules, Applicants disagree that Jacobsen teaches the other limitations of Claim 53.

Jacobson describes a method for detection, quantification and monitory the expression of mature microRNAs and small interfering RNAs. Jacobson describes the combination of a single strand target sequence with two tagging probes, each tagging probe containing an anchor sequence (See, e.g. Figure 9, paragraph [0027]). After they are combined, the tagging probe/target sequence is annealed and ligated. Forward and reverse primers, and a dual-labeled target detection probe are added to the ligated tagging probe/target sequence, and a quantitative PCR is performed.

Claim 53 depends from Claim 33. As described above, Claim 33 is directed towards a method for isolating a microRNA of interest from a sample with the microRNA of interest. The invention claims a capture probe with two adapter segments and a microRNA binding segment having a microRNA binding segment sequence. The microRNA binding segment of the capture probe is substantially complementary to, and capable of hybridizing to, one or more than one microRNA of interest by Watson-Crick base pairing. The 5' end of the first adapter segment is connected to the 3' end of the microRNA binding segment, and the 3' end of the second adapter segment is connected to the 5' end of the microRNA binding segment. The capture probe of the invention is similar to Jacobson's single strand target sequence with two tagging probes, each tagging probe containing an anchor sequence.

In the first step of the claimed method, a sample with the microRNA of interest is combined with a capture probe, and first linker and second linkers. Jacobson does not describe the use of first and second linkers.

The second step in the present invention, after the sample with the microRNA of interest, the capture probe, and first linker and second linkers are combined, the first linker hybridizes with the first adapter segment, the microRNA of interest hybridizes with the microRNA binding segment, and the second linker hybridizes with the second adapter segment. Jacobson does not describe the hybridization of first and second linkers to the first and second adapter segments.

In the third step of the present invention, the 3' end of the first segment is ligated to the 5' end of the microRNA of interest, and the 3' end of the hybridized microRNA of interest is

ligated to the 5' end of the hybridized second linker. This complex is defined as a strand of first linker, microRNA of interest and second linker that have been ligated together (ligated first linker- microRNA of interest-second linker) and hybridized to the capture probe. As set forth above, Jacobson does not describe the use of first and second linkers, and thus cannot describe this step.

Similarly, Jacobson does not describe the fourth step, where the capture probe is dehybridized from the strand of the ligated first linker- microRNA of interest-second linker. Nor does Jacobson describe the fifth step, where, the ligated first linker- microRNA of interest-second linker is purified from the capture probe, thereby purifying the microRNA of interest.

Adding methods for determining the methylation status of a cytosine in a nucleic acid sample described in Shapero and the modulation of synthesis or metabolism of multidrug resistance-associated protein as described in Baracchini to Jacobson does not cure the deficiencies of Jacobson. Therefore, since the combination of cited references would not result in the invention as claimed, Applicants respectfully submit that the references do not support a *prima facie* case of obviousness under the provisions of 35 U.S.C. §103. Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. §103 be withdrawn.

CONCLUSION

The Applicant believes that all pending claims are in condition for allowance and such action is earnestly requested. If the present amendments and remarks do not place the Application in condition for allowance, the Examiner is encouraged to contact the undersigned directly if there are any issues that can be resolved by telephone with the Applicant's representative.

If an extension of time is required to extend the time for filing a reply in the above-identified application, such extension is hereby requested.

The Director is hereby authorized to charge any fees which may be required to Deposit Account No. 19-2090.

Respectfully Submitted,

SHELDON MAK & ANDERSON

Date: April 30, 2012

By: /Laura M. Lloyd/
Laura M. Lloyd, Ph.D., J.D.
Reg. No. 54,461

SHELDON MAK & ANDERSON PC
100 Corson Street, Third Floor
Pasadena, California 91103-3842
Tel: (626) 796-4000
Fax: (626) 795-6321
E-mail: laura.lloyd@usip.com